ratios of 1:2:1 are referring. Applicant has deleted claim 2 and has included the pertinent matter in claim 1 and in proper Markush format. Additionally, as amended, the pertinent matter of claim 2 included in claim 1 now more clearly states to which polymers the claimed ratios of 1:2:1 are referring. Therefore, Applicant requests that this rejection be withdrawn.

Examiner has rejected claim 5 as it is unclear as to what the aging inhibitor is. Applicant respectfully refers the Examiner to the specification at page 3, lines 10-12, where reference is made to DE 37 43 949. This reference discloses suitable aging inhibitors such as tocopherol, substituted phenols, hydrochinones, 1,2-benzenediol and aromatic amines. Applicant respectfully submits that such aging inhibitors (i.e., anti-aging agents) as disclosed in that reference are well known to those skilled in the art and therefore additional disclosure in the present specification to this effect is not needed. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Examiner has rejected claims 13 and 14 as being unclear where the additional pressure-sensitive margin (PSA) layer is in relation to the reservoir. Applicant respectfully submits that one skilled in the art will know where the additional PSA layer is located after a thorough review of the claims. Both claims 13 and 14 are based on claim 1 which provides a transdermal therapeutic system in plaster form comprising a backing layer and a reservoir. The reservoir and the backing layer are sheet-like layers and are attached to each other. Therefore, one face of the plaster is formed by the backing layer and the other face of the plaster is provided by the reservoir. The latter face faces the patient's skin when applied and this is the only portion of the reservoir, as part of the

transdermal therapeutic system, where an additional pressure-sensitive adhesive layer and/or margin can be provided. Applicant believes that this would be clear to one skilled in the art. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Examiner has lastly rejected claim 15 as being incomplete for omitting essential steps. Applicant has amended claim 15 accordingly and therefore requests that this rejection be withdrawn.

Rejection of Claims 1-9 & 11-15 under 35 U.S.C. 103(a)

Claims 1-9 and 11-15 have been rejected as being unpatentable over any one of U.S. Patent No. 5,393,529 (Hoffman et al.), U.S. Patent No. 5,662,923 (Roreger), U.S. Patent No. 5,676,968 (Lipp et al.), U.S. Patent No. 5,683,711 (Fischer et al.), U.S. Patent No. 5,744,162 (Okabe et al.), U.S. Patent No. 5,906,830 (Farinas et al.) or U.S. Patent No. 6,153,216 (Cordes et al.) in combination with any one of U.S. Patent No. 4,954,343 (Hosaka et al.) or U.S. Patent No. 5,951,999 (Therriault et al.). It is respectfully submitted that these claims in their present form are patentably distinct from the prior art.

Referring to Hoffmann et al. '529, the reference teaches a plaster containing an estrogen (or its pharmaceutically acceptable derivative) alone or in combination with a gestagen. The active substances are at least primarily or completely dissolved in the adhesive, wherein the adhesive is based on homo- or copolymers with at least one derivative of acrylic or methacrylic acid, in combination with at least one water-swellable polymer (col. 3, line 21 to col. 4, line 50). However, nowhere in Hoffmann et al. is there a disclosure of amino-group containing polymers. Alternatively, Hoffmann et al. teaches the separate addition of crystallization inhibitors (col. 4, last paragraph). Nowhere in the

discussion of crystallization inhibitors are amino group-containing substances taught or disclosed.

Roreger '923 discloses self-adhesive plasters for the transdermal administration of steroid hormones. The self-adhesive plasters are characterized in that their active substance-containing pressure-sensitive adhesive layer comprises a pressure-sensitive hot melt adhesive and dexpanthenol in a concentration of 15 to 25% by weight. However, Applicant points out that nowhere is it taught in this reference that amino group-containing polymers are suitable for the plaster taught in Roreger '923 (Col. 2, lines 31-61). Roreger teaches that dexpanthenol serves as a particular substance to prevent crystallization of the active substance. Moreover, it is disclosed in Roreger that dexpanthenolin a concentration of at least 15% by weight is required in order to reliably prevent crystallization of the active substance in the formulation (col. 2, lines 16-19). Thus, Applicant contends that the minimum amount of dexpanthenol is much higher than the proportion of the crystallization inhibiting amino group-containing polymer of the present invention. Furthermore, Applicant submits that dexpanthenol and the amino group-containing polymer of the present invention are not interchangeable and therefore cannot be compared to one other.

Referring now to Lipp et al. '968, the reference teaches transdermal therapeutic systems with crystallization inhibitors which can allegedly be used in all known transdermal therapeutic systems (col. 2, lines 18-19). Lipp et al. teaches that suitable crystallization inhibitors are silicon dioxide or macromolecular substances such as polyvinylpyrrolidones, polyvinylalcohol, hydroxypropyl cellulose, ethyl cellulose, gelatin,

starch, dextrans, sterols or bile acids (col. 1, line 66 to col. 2, line 14). Applicant wishes to point out that nowhere in this reference is it taught that amino group-containing polymers, as defined by amended claim 1, can act as suitable crystallization inhibitors.

Turning now to Fischer et al. '711, the reference discloses an active ingredient patch wherein the concentration of at least one of the active ingredients is such that the saturation of the active ingredient is exceeded on application of the patch to the skin. The matrix contains a content of vitamin E, or a vitamin E derivative, and an active ingredient being at least one selected from the group of estrogen hormones and progestagenic hormones. Alpha-tocopherol is specified to be the essential component that prevents the active ingredient from crystallization. Although dimethylaminoethyl methacrylate is disclosed to be a suitable matrix polymer, the reference neither teaches nor discloses the specific compositions butyl methacrylate, 2-dimethylaminoethyl methacrylate and methyl methacrylate, or any of the other amino group-containing polymers of the present invention.

Okabe et al. '162 teaches a good stability of percutaneous absorption with time due to the absence of crystallization of the pharmacologically active substance in transdermal formulations. This is achieved by polymer comprising lipophilic monomer units and hydrophilic monomer units in a specific ratio (see Abstract). The ratio by weight is specified as being between 98:2 and 0:100. The reference provides that hydrophilic monomers can be (meth)acrylamide and N,N-dimethylacrylamide, but polymers with amino groups are not disclosed therein.

Farinas et al. '830 discloses that polyvinylpyrrolidone, cellulosic polymers, polyethylene oxide, polyvinyl alcohol, polyacrylic acid, gelatins, cyclodextrins and silica can serve as crystallization inhibitors (col. 8, lines 14-20). Farinas et al. further discloses that a variety of physically and chemically compatible polymeric materials can be employed as pressure-sensitive adhesives. Polyacrylates are named among other polymers such as polysiloxanes, polysobutylenes, polyurethanes or EVA copolymers, but with no mention of the amino-group containing polymers of the present invention.

Turning now to Cordes et al. '216, the reference teaches that the addition of small amounts (about between 1.3 and 3.5%) of oxtyldodecanol was surprisingly found to prevent crystallization of estradiol and noresthisterone from supersaturated matrices (col. 4, lines 54-60). This effect was observed for a pressure-sensitive adhesive matrix being a vinylacetate containing acrylate copolymer (col. 3, lines 66-67), and there is no mention of amino group-containing polymers therein.

Referring now to Hosaka et al. '343, the reference teaches a dermal pharmaceutical preparation that keeps the drug in a dissolved state and is excellent in drug liberation and adhesion to the skin (Abstract). The pharmaceutical preparation comprises a pressure-sensitive adhesive which is a copolymer comprising a (meth)acrylamide as a comonomer unit, the (meth)acrylamide having an amino group to achieve the desired properties (Abstract). The (meth)acrylamide is represented by formula (I) at the bottom of col. 2. It is further specified that R1 represents a hydrogen atom or a methyl group, R2 represents an alkylene group, and R3 and R4 each represent a hydrogen atom, an alkyl group or a phenyl group (col. 3, lines 1 to 4). Although it is

repeatedly pointed out in this reference that the (meth)acrylamide has an amino group, Applicant contends that it would be evident to one skilled in the art that an amino group is only present in the (meth)acrylamide according to formula (I), if both R3 and R4 represent a hydrogen atom. It is Applicant's position that in all other cases a (meth)acrylamide according to formula (I) comprises an amine group rather than an amino group. Therefore, Hosaka et al. '343 teaches that copolymers with amine groups are suitable to keep a drug in a dissolved state, but does not teach that copolymers comprising an amino group might serve as a crystallization inhibitor as well.

According to Hosaka et al. '343, the drug which can be used in a dermal pharmaceutical preparation is not particularly limited (col. 3, lines 50-53). However, it is further disclosed in Hosaka et al. that the pressure-sensitive adhesive markedly increases the capability of dissolving hydrophilic drugs, of which numerous are provided (col. 3, line 55 to col. 4, line 28). Applicant contends that all examples were carried out with hydrophilic drugs. In addition, it is explained therein that the pressure-sensitive adhesive has a markedly increased polarity due to the amido group and amine group (which is incorrectly designated as an amino group) of the (meth)acrylamide (col. 3, lines 32-37).

Applicant respectfully submits that since estradiol is not a hydrophilic drug, one skilled in the art would not expect to successfully prevent crystallization of estradiol using a pressure-sensitive adhesive comprising a markedly increased polarity by means of (meth)acrylamide comonomers containing amido and amine groups, nor by amino-group containing polymers. Therefore, Applicant believes that it would not be obvious to one skilled in the art, in light of Hosaka et al., to replace the crystallization inhibitors

why ?

according to any of the aforementioned references with an amino group-containing polymer, if a combination of estradiol and noresthisterone acetate are to be administered by a transdermal therapeutic system.

Applicant additionally points out that acrylamide is a neurotoxin and a carcinogen that is able to penetrate the skin. Thus, considerable efforts have to be made in order to remove all acrylmide monomers from the resulting pressure-sensitive adhesive in order to achieve a matrix which will be allowed by health authorities for medicinal purposes. Such efforts are quite costly and can be circumvented if matrices according to the present invention are used for transdermal therapeutic systems.

Turning lastly to Therriault et al. '999, the reference discloses a pressure-sensitive adhesive for transdermal hormone delivery systems which reduces the tendency of the hormones to crystallize within the transdermal delivery system. The pressure-sensitive adhesive essentially comprises a (meth)acrylic ester backbone copolymer wherein the non-tertiary alcohol portion has 1 to 30 carbon atoms. Thus, Applicant submits that one skilled in the art may be tempted to combine the pressure-sensitive adhesive of Therriault et al. with the crystallization inhibitors disclosed in any one of the aforementioned references, rather than replacing them.

However, according to Therriault et al., a so-called "C monomer" can optionally be present in the copolymer. This C monomer is specified to have the formula X-Z (col. 3, line 15), wherein the X moiety may comprise an amine (col. 3, line 31) and the Z moiety may be formed from t-butyl acrylates (col. 4, line 10) or vinyl unsaturated amides (col. 4, line 17). Thus, Therriault et al. does not provide any information or guidance

which would make the use of amino group containing-polymers as inhibitors of crystallization obvious to one skilled in the art.

Applicant respectfully submits that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references when combined must teach or suggest all of the claim limitations (emphasis added). Any one of Hoffman et al. '529, Roreger '923, Lipp et al. '968, Fischer et al. '711, Okabe et al. '162, Farinas et al. '830 or Cordes et al. '216 in combination with any one of Hosaka et al. '343 or Therriault et al. '999 neither teaches nor suggests each and every element of the present invention. It is therefore respectfully requested that the application defined in the claims is patentably distinguishable over the art under 35 U.S.C. 103(a).

Applicant does contend that the field of transdermal therapeutic systems for the application steroid hormones is well developed, as indicated by the numerous cited references and that various crystallization inhibitors are disclosed in the prior art. However, Applicant respectfully submits that the problem solved by the present invention is not taught, disclosed, or solved by any of the cited references in combination with any other. The present invention seeks to make available an alternative crystallization inhibitor for transdermal therapeutic systems containing a combination of estradiol and noresthisterone acetate as therapeutically active substances. In addition, it provides the use of amino group-containing polymers as constituents of a matrix that is prepared using polyacrylate pressure-sensitive adhesives. This particular feature of the present invention

is not suggested, disclosed or taught by any of the cited references, alone or in any combination, and therefore any combination thereof would not teach each and every limitation of the present invention. Furthermore, Applicant contends that any combination with Hosaka et al. would not be obvious because there would be no reasonable expectation of success. As explained above, one skilled in the art would not expect to successfully prevent crystallization of estradiol using a pressure-sensitive adhesive comprising a markedly increased polarity by means of (meth)acrylamide comonomers containing amido and amine groups, nor by amino-group containing polymers as estradiol is not a hydrophilic drug.

For the foregoing reasons, it is respectfully submitted that the present application is in condition for allowance, and such action is earnestly solicited. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

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